Bandolier 86

What do we think?
What do we know?
What can we prove?

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The fat police and the cholesterol fairy

Myths that go bump in the night. Those of you who take tablets will know what a pain it is to remember to take them, especially for an asymptomatic condition. Some people use the Barker and Dobson principle - tip all the tablets into a jar, then dole out 'enough' for the day. Every so often comes a quirk, albeit a plausible quirk.

Take your statin at night. Why? Because the cholesterol fairy gets all busy at night, doing her cholesterol shovelling then. ***Bandolier*** has been digging too, and can't find the evidence. It might just be that the fairy comes to life at night. But if you take a once a day drug for ever you might expect that the peaks and troughs would be smoothed out. One of the five statins on the market does not mention evening or night, but still can combat the cholesterol fairy. It is much, much, easier to take all your once a day medicines at the same time. Either all should be spooned out at night time, or the statin moves to morning with the others. Perhaps it's all down to boring stuff like pharmacokinetics, but ***Bandolier*** has failed to find the fairy.

Close, but no cigar

Many of you have asked for more on adverse effects, after ***Bandolier*** 85. Why is it so difficult for even professionals to obtain credible incidence data on adverse effects? Patients rightly ask will it work? and will it do me any harm? Our answers to the efficacy question have improved beyond recognition, or at least the evidence has, but our answers about harm fall way short. ***Bandolier's*** example for you this month is urticaria with ACE inhibitors. What is the incidence, and is it a class phenomenon?

Andrew's mother's hairdresser's friend picks and chooses

One of life's great sports is rebutting meta-analyses that conflict with your deeply-held beliefs. One method is to say that the patients included in the meta-analysis are different from our patients. The sound of moving goal posts often accompanies this strategy, as disbelievers search desperately for any difference, because, of course, they don't like the evidence and don't want to believe it. In contrast, we may be less than fastidious when we do like the evidence.

So two examples this month from meta-analyses which show how sensitivity analysis can help us over or around our prejudices. One from nicotine replacement therapy shows how robust the evidence is for patch, but not gum. Another comes from the anaesthetists. Using epidurals or spinals as well as a general anaesthetic reduces mortality says a meta-analysis. Yes, but only when a few small trials from decades ago with unreasonably high death rates (over 15%) were included. With patients like ours, death rates below 3%, there's no effect.

Bandolier Internet update

Some major moves this month to increase the electronic resource that ***Bandolier*** aims to become.

- The **migraine** site sponsored by MSD has grown substantially, though we still can't find good evidence on trigger factors.
- With sponsorship from the BUPA Foundation and in collaboration with the Cochrane PaPaS group we have launched a new **Palliative and supportive** care site.
- **Healthy Living** has over a dozen new stories, with some impressive stuff on the benefits of certain types of alcohol, again backed by the BUPA Foundation.
- With new sponsorship from AstraZeneca, a new site on **Atrial Fibrillation** will open soon.

All the specialist subsites are available from the home page (address below), as well as screen, and downloadable facsimile versions, of every issue of ***Bandolier*** and ***ImpAct***, and much else. There's ***Bandolera***, our Spanish language version, and the Oxford Pain Internet Site in Spanish.

BioMed Central

This new electronic journal is just the bees knees for systematic reviews and meta-analysis because there is no restraints on space. Two articles from BioMed are mentioned in this issue of ***Bandolier***. It's great for systematic reviews and meta-analysis because there is lots of detail there in tables, and submission to publication is about three months. Each paper comes in PDF format to print and read over coffee. Try it at www.biomedcentral.com.

In this issue

Bandolier's **electronic resources at www.ebandolier.com**

Low dose aspirin – harm and benefits

By now most people are aware that aspirin and NSAIDs are associated with an increased risk of upper gastrointestinal bleeding, and the risk with NSAIDs has been carried before (***Bandolier*** 52, 79). A question still asked though, concerns the risk associated with low dose aspirin (75 mg up to 300 mg a day) used in the secondary or primary prevention of heart disease or stroke. A new epidemiological study [1] and meta-analysis [2] may help.

Risk of bleeding with low-dose aspirin

A case-control study was conducted using the UK General Practice Research Database that contains details of patient demographics, medical histories and diagnoses, referrals and prescriptions. The UKGPRD is becoming an important research tool, used frequently by researchers from all over the world. The authors of the aspirin study were based in Madrid.

The source population were patients aged 40 to 79 years with the same GP for at least two years. Cases were identified as those with upper gastrointestinal bleeding or perforation, excluding those with cancer, varices, liver disease, or alcoholism, or with other obvious reasons why they may have had a propensity for gastrointestinal bleeding. For inclusion a case had to have a specific site of bleeding located in stomach or duodenum or a clinical diagnosis of peptic ulcer, and be referred to a specialist or admitted to hospital. Paper records confirmed the accuracy of the computer diagnoses. Controls were selected at random and matched for age, sex and year, and with the same exclusion criteria.

Current users were defined as use within 30 days, recent users between 31 and 180 days, and past users longer than 180 days before the incident date. Exposure to other drugs was noted and analysed. Results were adjusted for a variety of covariates using logistic regression to compute a relative risk.

Results

There were 2,105 cases and 11,500 controls. They were well matched for age and sex. Two-thirds were men older than 60 years. The indication for aspirin use was predominantly for secondary prevention of coronary or cerebrovascular disease (about 80% of the time) in cases and controls. The most common dose prescribed was 75 mg (48%), 150 mg (27%) or 300/325 mg (19%). Only in 6% of people was the prescribed dose more than this.

For current users of low-dose aspirin the relative risk of upper GI bleeding was 2.0 (95% confidence interval 1.7 to 2.3). The risk diminished when aspirin had not been used for 180 days or more (Figure 1). The risks were the same for fatal or non-fatal bleeding, for men or women, and for age groups 40-59 years, 60-69 years and 70-79 years. There was no difference for risk associated with site of bleeding.

Figure 1: Upper GI bleed with low-dose aspirin according to recency of use

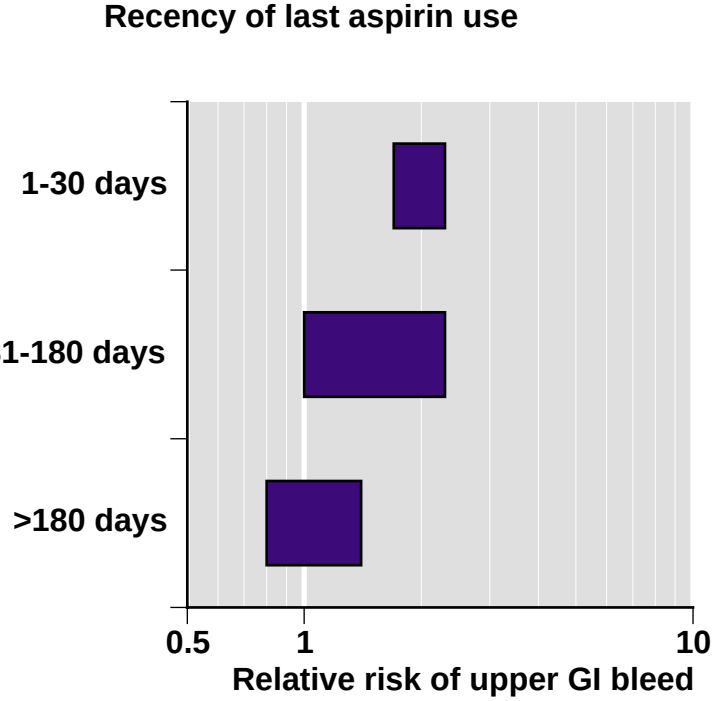


Figure 2: Upper GI bleed with low-dose aspirin according to duration of use

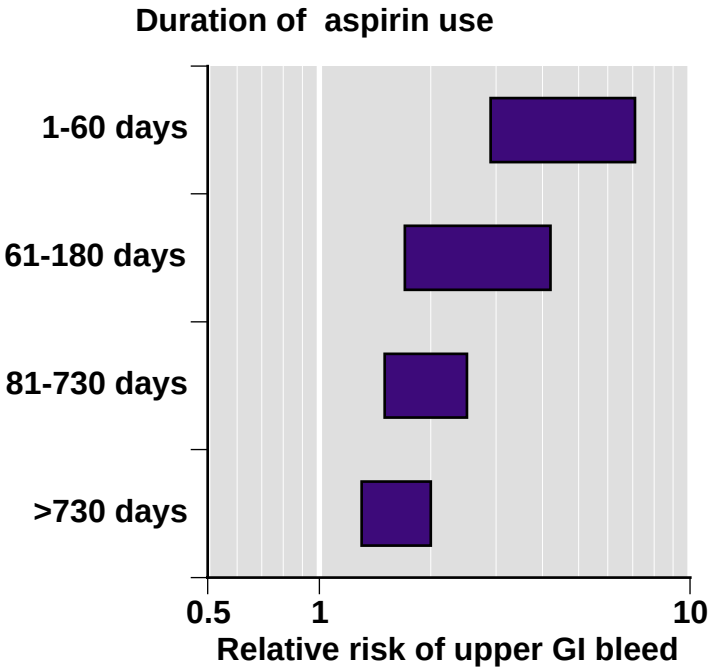
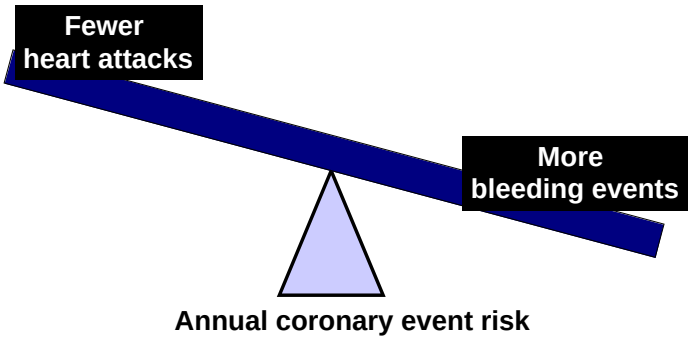


Table 1: Upper GI bleed with low-dose aspirin according to formulation

		Adjusted relative risk (95% CI)
All sites	Plain	1.9 (1.6 to 2.3)
	Coated	2.3 (1.6 to 3.2)
Gastric	Plain	2.0 (1.5 to 2.5)
	Coated	2.2 (1.4 to 3.6)
Duodenal	Plain	1.6 (1.3 to 2.1)
	Coated	2.2 (1.4 to 3.4)



Formulation

Enteric-coasted aspirin had a similar risk associated with upper GI bleeding or perforation to plain aspirin (Table 1).

Dose

There was a hint of a dose-response over a limited dose-range with a higher risk of upper GI bleeding at doses above 300 mg daily, but this was based on a very small number. There was no appreciable dose response below 300 mg.

Drug interactions

Using aspirin together with high-dose NSAID increased the risk of upper GI bleeding substantially, with a relative risk of 13 (9 to 21), beyond the sum of the independent effects. Interaction were only additive at low or medium doses of NSAIDs. There was no apparent interaction between aspirin and paracetamol or aspirin and steroids.

Duration effects

There was an indication that the risk of upper GI bleed with low-dose aspirin was greater in the first two months of use than with use over a longer time period (Figure 2).

Aspirin for primary prevention

A question frequently asked of ***Bandolier*** concerns the appropriateness of using low-dose aspirin in the primary prevention of cardiovascular disease. Which patients are likely to benefit? A new meta-analysis from Sheffield, with some clever thought behind it, goes most of the way to telling us.

The problem, simply put is this. Aspirin may reduce the number of heart attacks, but it can, at the same time, increase the number of bleeds, both gastrointestinal bleeds and perhaps strokes. Is there some point at which the benefits outweigh the risks, or vice versa?

Meta-analysis

The meta-analysis was of randomised trials of aspirin for primary prevention. Studies had also to give information on total cardiovascular events, myocardial infarction, stroke, bleeding complications, and all cause mortality.

There were four studies with 48,500 people, 25,000 of whom were given 75-500 mg aspirin daily. Only one trial included women. Trial duration was 3.8 to 6.8 years.

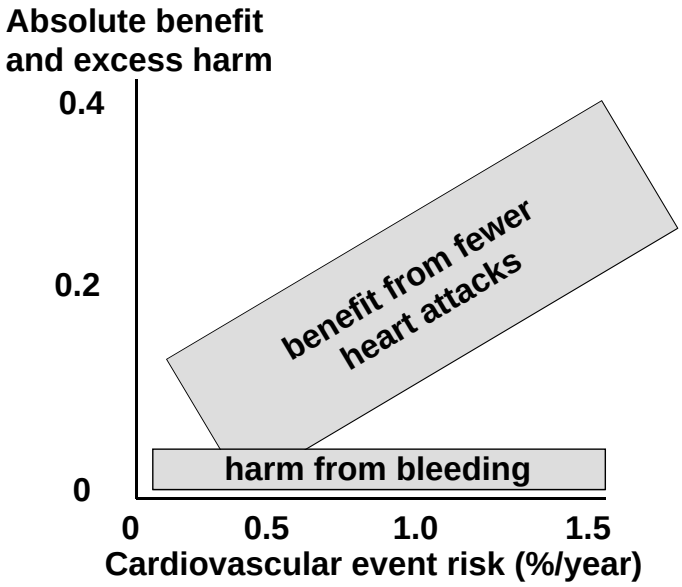
Results

Table 2 shows the weighted mean results from the four trials for a variety of outcomes, as the absolute risk per year of the event in the control group, the absolute benefit or harm, and the odds ratio. Clearly low dose aspirin reduced cardiovascular events and heart attacks but increased haemorrhage, non-cerebral bleeds and non-minor bleeds (all non-cerebral bleeds not classed as minor). It was interesting that the odds ratio for the increase in bleeding events caused by low dose aspirin in this meta-analysis (odds ratio about 1.7) was similar to the increase found in the case-control study [1] (relative risk 2.0).

The authors then set out to calculate the ***net*** benefit by calculating the number of heart attacks prevented net of bleeding events at different levels of baseline risk for cardiac

Table 2: Benefit and harm from low dose aspirin in a meta-analysis

Event	Absolute risk in control group (Percent/year)	Absolute benefit from aspirin (Percent per year)	Odds ratio (95% CI)
Cardiovascular events	0.92	0.13	0.85 (0.78 to 0.94)
Myocardial infarction	0.52	0.15	0.70 (0.62 to 0.79)
Strokes	0.29	-0.02	1.06 (0.91 to 1.24)
All cause mortality	0.73	0.05	0.94 (0.85 to 1.04)
	Absolute risk in control group (Percent/year)	**Absolute harm from aspirin (Percent per year)**	**Odds ratio (95% CI)**
Best overall estimate of haemorrhage	0.13	0.09	1.69 (1.38 to 2.07)
Major non-cerebral bleeds	0.05	0.04	1.73 (1.14 to 2.63)
Non-minor bleeds	0.22	0.18	1.77 (1.40 to 2.25)



events. This was done on the basis of 100 patients treated for five years with low dose aspirin at annual risk levels of 0.5%, 1% and 1.5% a year. The assumption was that low dose aspirin reduced the risk of MI by 30%, but that the risk of bleeding was constant. They also give the number of patients needed to be treated with low dose aspirin over five years to prevent one event.

These results are in Table 3. At a low risk, 0.5% a year, 133 people have to be treated with low dose aspirin for five years to prevent one myocardial infarction. But as we take into account the increased risk of cerebral haemorrhage, major bleeds and non-minor bleeds, the NNT increases until eventually it becomes an NNH so that eventually one person is ***harmed*** for every 500 treated. The results look better with increasing cardiovascular risk.

Comment

Together these two papers help us think our way through the problems around the use of aspirin in primary prevention. We may know that aspirin is a good thing for preventing heart attacks, but the risk of harm from bleeding is not negligible, even at the low doses used. The balance tips to benefit over harm when the annual risk of a cardiovascular event is 1% or above (the authors say ≥0.8%), and the Sheffield Tables for Primary Prevention allow the risk to be calculated.

Their conclusion was that aspirin for primary prevention is safe and worthwhile at a coronary risk of 1.5% a year or more, safe but of limited value at a coronary risk of 1% a year, and unsafe at a coronary risk of 0.5% a year. Those with Sheffield Tables to hand will know that this means that primary prevention with aspirin makes no sense unless the patient is "bad enough" to be "on" the Sheffield tables. We have to remember that aspirin, like all other drugs, is a poison [3].

References:
1 FJ de Abajo, LA García Rogríguez. Risk of upper gastrointestinal bleeding and perforation associated with low-dose aspirin as plain and enteric-coated formulations. BMC Clinical Pharmacology 2001 1:1 (www.biomedcentral.com/1472-6904/1/1)
2 PS Sanmuganathan et al. Aspirin for primary prevention of coronary heart disease: safety and absolute benefit related to coronary risk derived from meta-analysis of randomised trials. Heart 2001 85: 265-271).
3 Tramèr MR. Aspirin, like all other drugs, is a poison. BMJ 2000 321: 1170-1171.

Table 3: Benefit and harm from low dose aspirin: overall absolute benefits and NNTs

	CHD event risk					
	0.5%/ year		1.0%/ year		1.5%/ year	
Myocardial infarcts prevented	Absolute reduction (%/year)	NNT	Absolute reduction (%/year)	NNT	Absolute reduction (%/year)	NNT
Total	0.75	133	1.5	67	2.25	44
Net of 0.19 cerebral haemorrages	0.56	179	1.31	76	2.06	49
Net of 0.17 major bleeds	0.39	256	1.14	88	1.89	53
Net of 0.76 non-minor bleeds	-0.20	-500	0.55	182	1.3	77

Numbers are calculated on basis of treating 100 patients for five years. NNT is the number of patients needed to be treated for five years to prevent one event. Negative values show number of patients needed to be treated to harm one patient

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NICOTINE REPLACEMENT THERAPY FOR STOPPING SMOKING

Bandolier 54 examined a Cochrane review of nicotine replacement therapy. Since then the review has been updated, nicotine replacement therapy (NRT) is much higher on the political agenda, and the way we look at data has changed a bit, so we thought it worth another look, together with some cost-effectiveness.

Review

The Cochrane review [1] is typically thorough because the Cochrane Tobacco Addiction Group has its own ongoing register of trials that is being constantly updated. This review was of trials available up to April 2000. Included were randomised trials in which NRT was compared to placebo or no treatment, or where different doses of NRT were compared. Excluded were trials not reporting cessation rates or with follow-up of less than six months.

The main outcome measure was abstinence from smoking after at least six months of follow-up. The most rigorous definition of abstinence for each trial was used, with biochemically validated rates if available. The meta-analysis used fixed effects odds ratios, but since those lack intuitive meaning, ***Bandolier*** reports NNTs together with absolute quit rates.

Results

The main results are in Table 1, for all trials, for large trials (those with combined placebo plus NRT patients of at least 250), and for low baseline quit rates of less than 10%. These sensitivity analyses seemed additionally useful to test the validity of the results, because many of the NRT trials included in the review were small (fewer than 100 patients) and the range of quit rates without NRT was wide (2-46% with gum, for instance).

Numbers needed to treat for nicotine replacement versus placebo or no treatment controls were of the order of 8 to 17 for different NRT preparations using all trials. There were many trials and patients for gum and patch, but limited numbers for intranasal sprays, inhalers and sublingual tablets (Table 1). Between 8% and 13% of patients stopped smoking at 6-12 months without NRT, and this increased to 14% to 24% with NRT.

Only gum and patch had trials of over 250 participants. The NNT for patch was 17 for all trials and 17 for large trials. For gum, the NNT of 12 for all trials rose to 17 for large trials.

Only gum and patch had sufficient trials with controls cessation rates of less than 10% for analysis. The NNT for patch was 17 for all trials and 17 for trials with lower cessation rates. For gum, the NNT of 12 for all trials rose to 36 for control cessation rates below 10%.

Table: Results from nicotine replacement therapy meta-analysis with sensitivity analysis

		Patients stopped smoking at 6-12 months				
		NRT		Placebo		
Type of NRT	Number of trials	Number/total	Percent	Number/total	Percent	NNT (95% CI)
All trials						
Gum	48	1453/7387	20	1084/9319	12	12 (11 to 14)
Patch	31	1384/9708	14	495/5969	8	17 (14 to 20)
Intranasal spray	4	107/448	24	52/439	12	8 (6 to 14)
Inhaler	4	84/490	14	44/486	8	12 (8 to 26)
Sublingual tablet	2	49/243	20	31/245	13	13 (7 to 103)
Large trials						
Gum	18	792/5126	15	710/7308	10	17 (14 to 22)
Patch	14	1115/8333	13	352/4615	8	17 (15 to 21)
Cessation rate with control<10%						
Gum	15	299/3370	9	315/5192	6	36 (25 to 61)
Patch	17	482/4219	11	193/3440	6	17 (14 to 22)

Large trials were those with more than 250 participants in NRT and placebo groups combined

Comment

The overall result for the updated Cochrane review is similar to that obtained previously. We can be sure that nicotine patches will almost double the number of people stopping smoking at six to 12 months. For every 17 people using nicotine patch for about eight weeks to help smoking cessation, one more will stop smoking who would not have done with no patch or with placebo patch.

The background rate of cessation of smokers in general is estimated at about 1.5% a year. In the control groups in these trials, the rate of cessation is often much higher than this, showing that people wanted to stop smoking, and that personal motivation with some professional intervention can achieve a certain amount on its own. Nicotine patches can almost double the rate, which must be good. The evidence for patches is robust to sensitivity analysis, and based on a large number of trials and patients.

The evidence for gum is a bit flakey, because the NNTs increase substantially with larger trials and in those with lower control cessation rates. Inhalers and sprays look effective but based on relatively small numbers of trials and patients.

Cost effectiveness

So if nicotine patches are prescribed in general practice, is this a good buy for health services? The argument would be that the known effects of smoking are so awful, that by stopping people smoking we ***buy*** further years of life. So we should be able to compute how much the intervention(s) cost, how many life years we obtain, and therefore the cost per life year.

This has been done [2] off the back of a trial in which 4.5% of people stopped smoking with GP counselling, and 9.6% stopped with counselling plus nicotine patches (NNT 20). In the trial only one of 476 smokers who were still smoking at the end of the first week of treatment were abstinent at one year. Calculations were therefore based on a model that only allowed nicotine patches for a week in those who were still smoking (based on breath carbon monoxide measurement).

The cost per life year saved was £344 to £785 depending on the age of the patient. Other studies [3] come up with similar estimates. When examined against a library of life-saving interventions [4], nicotine replacement therapy is pretty cost-effective.

References:

1 C Silagy et al. Nicotine replacement therapy for smoking cessation (Cochrane Review). In: *The Cochrane Library,* Issue 1, 2001. Oxford: Update Software.

2 JA Stapleton et al. Prescription of transdermal nicotine patches for smoking cessation in general practice: evaluation of cost effectiveness. Lancet 1999 354: 210-215.

3 S Parrots et al. Guidance for commissioners on the cost-effectiveness of smoking cessation interventions. Thorax 1999 53 (Suppl 5): S1-S38.

4 TO Tengs et al. Five-hundred life-saving interventions and their cost-effectiveness. Risk Analysis 1995 15:369-390.

More on MMR and autism

If you came to a small Oxfordshire village during the day and counted the number of lights that were on, you would find few. Come at night and you would find many. One conclusion might be that putting the lights on has caused it to become dark. Part of the MMR-autism debate (***Bandolier*** 84) has involved a similar observation, that autism was rare and now is common, and MMR was rare and now is common. Presto, MMR causes autism!

It may be a bit more complicated than that. Two new studies [1,2] have examined the temporal relationship between MMR vaccination rates and autism. Autism is on the increase despite high and stable MMR vaccination rates.

UK study

One study from Boston is based on the UK General Practice Research Database. It identified 305 children (254 boys) aged 12 or younger whose diagnosis of autism was first recorded between 1988 and 1999. The peak age of first diagnosis was at years 3 and 4, but with a substantial number being diagnosed at six years or older. The number of cases and incidence of autism increased substantially and constantly over the period (Figure).

The study included a detailed analysis of 114 boys born in 1988-1993 who had a first recorded diagnosis of autism at ages 2-5 years. For them the four-year risk of diagnosed autism rose from 8 per 10,000 for boys born in 1988 to 29 per 10,000 for boys born in 1993 while the MMR vaccination rate was constant at about 97%.

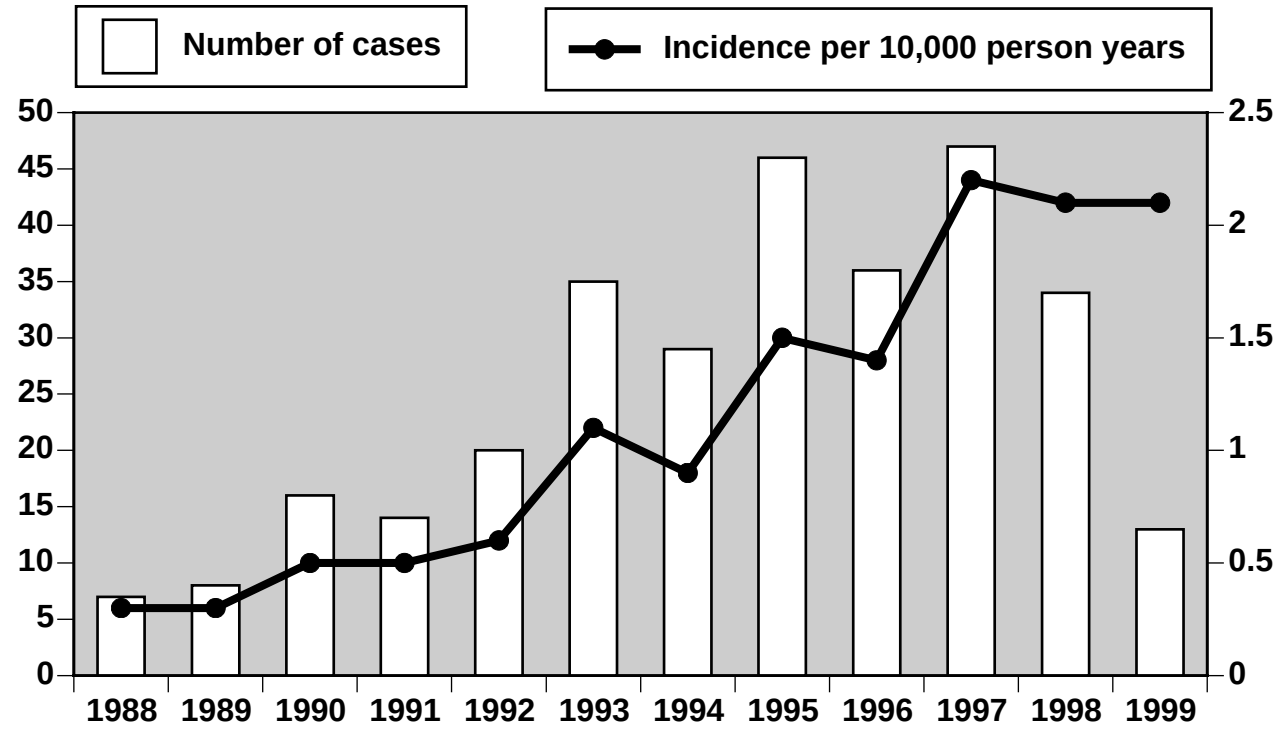
California study

The California study used data from 21 Regional centres covering all of California, and for the years 1980 to 1994. MMR immunisation rates by two years of age were about 72% before 1988 and about 82% afterwards, with the same preparation used since 1979. During this time the number of cases of autism, about 200 in 1980, increased inexorably to about 1200 by 1994. The trend for increasing autism in California persisted long after the introduction of MMR vaccination, and was not affected by a modest increase in immunisation rates in the mid 1980s.

Comment

This continuous upward trend in autism dating from the late 1970s or early 1980s has been seen before in a study from North Thames [3]. We now have three studies, all showing this inexorable rise irrespective of whether immunisation rates are high and uniform, or pretty high and getting higher.

Figure: Total number of cases of autism and incidence per 10,000 person years in UK



MMR has been available and been used for years. None of these studies supports, and all refute, that autism is caused by MMR vaccination, or that MMR vaccination is responsible for a major number of cases of autism.

What these studies all confirm is that autism, especially among boys, is on the increase. We don't know why. There is a plan for a further large case-control study using the UKGPRD [4]. It is predominantly to examine the link between MMR and autism, but may provide clues about links with environmental or other factors linked with autism.

References:
1 JA Kaye et al. Mumps, measles, and rubella vaccine and the incidence of autism recorded by general practitioners: a time trend survey. BMJ 2001 322: 460-463.
2 L Dales et al. Time trends in autism and in MMR immunization coverage in California. JAMA 2001 285: 1183-1185.
3 B Taylor et al. Autism and measles, mumps, and rubella vaccine: no epidemiological evidence for a causal association. Lancet 1999 353: 2026-2029.
4 L Smeeth et al. A case-control study of autism and mumps-measles-rubella vaccination using the general practice research database: design and methodology. BMC Public Health 2001 1:2 (www.biomedcentral.com/1471-2458/1/2)

WHICH ANAESTHETIC TECHNIQUE?

General anaesthesia involves using gases and intravenous drugs to send us to sleep and keep us asleep. Injection of local anaesthetic drugs in or around the spine constitutes neuraxial blockade and may confer additional benefits. Is there any difference between them in terms of harmful outcomes? A meta-analysis suggests there may be, but it is also an object lesson in caution and sensitivity analysis. It is also important because it helps us think about rare but serious adverse events (***Bandolier*** 85).

Review

The review was exemplary in the way it searched for papers, found additional information, contacted authors, and extracted data. The aim was to find all trials where patients were randomised to neuraxial blockade or not. Patients receiving neuraxial blockade could also have general anaesthesia. Considerable effort went into extracting all useful data, but here we concentrate on mortality within 30 days of randomisation.

Results

There were 141 trials with 9,559 patients. There were 247 deaths within 30 days, recorded in 35 trials. There were nine trials with at least 10 deaths per trial, and these are shown in the Figure as a L'Abbé plot. For only three of these smaller trials was there a large effect of neuraxial blockade, and in these three there was an extraordinarily high death rate with control of over 15%. For six other trials in which the death rate with control was below 15%, the death rates with neuraxial blockade and control were about the same.

This could be interpreted as some form of heterogeneity, and the L'Abbé plot was first suggested as an aid to detecting whether or not all trials in a meta-analysis were giving the same sort of result. Clearly here they were not.

So some sensitivity analysis would seem in order. Much sensitivity analysis according to methodological issues had been done in the original paper, but not one according to

Table: Mortality with neuraxial blockade and control in a meta-analysis and sensitivity analysis

Condition	Trials	Patients (% total)	Deaths/Total (%) Neuraxial blockade Present	Deaths/Total (%) Neuraxial blockade Absent	Relative risk (95% CI)	NNT (95% CI)
All trials	141	9559 (100)	103/4871 (2.1)	144/4688 (3.1)	0.7 (0.5 to 0.9)	98 (60 to 265)
Trials with fewer than 10 deaths	132	7067 (74)	32/3537 (0.9)	44/3530 (1.2)	0.7 (0.5 to 1.2)	n/c
Trials with more than 10 deaths	9	2492 (26)	71/1334 (5.3)	100/1158 (8.6)	0.6 (0.5 to 0.8)	30 (19 to 77)
More than 10 deaths, **more** than 100 patients (death rate in control **<**10%)	4	1889 (20)	49/1054 (4.6)	48/835 (5.7)	0.9 (0.6 to 1.4)	n/c
More than 10 deaths, **fewer** than 100 patients (death rate in control **>**10%)	5	603 (6)	22/280 (7.9)	52/323 (16.1)	0.5 (0.3 to 0.8)	12 (7.5 to 32)
All trials with a death rate with control of less than 10%	136	8956 (94)	81/4591 (1.8)	92/4365 (2.1)	0.8 (0.6 to 1.1)	n/c

n/c = NNT not calculated because no significant difference on relative risk

event rates. The Table shows the results obtained for all 141 trials, and for those with more or fewer than 10 deaths. Clearly the latter show the largest treatment effect.

In those trials with more than 10 deaths, four with more than 100 patients per group have a death rate of below 10% and show no statistically significant effect of neuraxial blockade. Five trials had fewer than 100 patients per group and a death rate with control of over 10%, and show a very large effect.

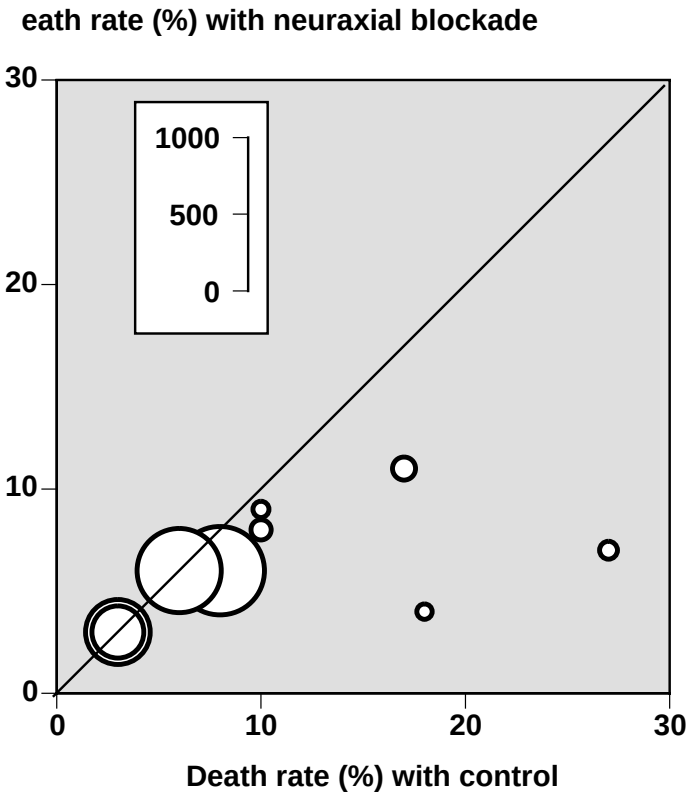
If we exclude all trials with death rates of over 10% from the combined analysis, then the effect of neuraxial blockade is very small, perhaps reducing the death rate from 2.1% to 1.8%, a reduction that is not statistically significant, but in 136 trials with 94% of the patients.

Comment

When interpreting results of clinical trials or meta-analyses to our patients, we are told to ask whether the patients in the trial or analysis are like our patients, in terms of demography or severity of disease. Here we find that an apparent overall beneficial effect of neuraxial blockade derives from a few small trials with exceptionally high death rates, three of which were published in the early 1980s. When we exclude these, no statistical effect remains.

Few surgical procedures have death rates above 10%, and it is pertinent to ask whether these results apply to our patients. The authors of the meta-analysis are understandably cautious over any claims, and the aim here is not to argue against the use of neuraxial blockade in anaesthesia. Rather it is to use this as an example of justified caution of where an overall conclusion can be influenced by a few small and unrepresentative trials.

Figure: L'Abbé plot of nine trials with at least 10 deaths



References:
1 A Rodgers et al. Reduction in postoperative mortality and morbidity with epidural or spinal anaesthesia: results from overview of randomised trials. BMJ 2000 321: 1-12.